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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/308,027 | 08/16/1999 | TOSHIO SONE | 06501/031001 | 5615 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | 19 |

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/308,027 | Applicant(s) SONE ET AL. | |
|---|---|---|---|
| | Examiner " Neon" Phuong Huynh | Art Unit 1644 | |

*-- The MAILING DATE of this communication app ars on th cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17* is/are allowed.

6)☒ Claim(s) *16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 16-17 are pending.

2. In view of the amendment filed 9/11/02, the following objections and rejections remain.

3. The drawings, filed 8/16/99, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review mailed 3/12/02. Appropriate action is required. It is noted that Applicants will submit formal drawings subsequent to receipt of Notice of Allowance.

4. The disclosure is objected to under 37 CFR 1.821(d) because of the following informality: (1) the second paragraph on page 23, line 14 and 17 requires SEQ ID NO, (2) the first paragraph on page 25, lines 1-5 also require SEQ ID NO, (3) "p66-80, 9186-200, p236-250 and p341-355 on page 23, line 17 requires SEQ ID NO.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) A method and a customized pharmaceutical composition for **treating** Japanese cedar pollen allergy in a subject in needed thereof; the method comprising: (a) identifying an HLA class II molecule expressed by the subject; (b) selecting an antigenic peptide derived from Japanese cedar pollen allergen Cry J j 1 or Japanese cedar pollen allergen Cry j2 wherein the antigenic peptide binds to the HLA class II molecule and wherein: (1) when the HLA class II molecule identified in step (a) is such as the ones recited in (1) through (8) of claims 16, and 17, **does not** reasonably provide enablement for (1) a method for "preventing" Japanese cedar pollen allergy in a subject as recited in claim 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a method for identify T cell epitope in Cry j 1 and Cry j 2 using T-cell clone derived from patients who suffer from cedar pollen allergy and the T-cell proliferation response is determined by tritiated thymidine incorporation and (2) a method for treating Japanese cedar pollen allergy by identifying HLA class II molecule expressed by the subject, selected the appropriate antigenic peptide such as SEQ ID NO: 1, 5, 7, 9, 10, 21, 23, 142, 2, 8, 15, 17, 22, 3, 4, 14, 19, 6, 12, 16, 20, 18, 13 and 19 that binds to the appropriate HLA class II molecule and administer the selected antigenic peptides mentioned above to the subject. Example 10 shows identification of T-cell epitope in CB6F1 mice by immunized the mice with Cry j2 peptides such as SEQ ID NO: 14 and 19 recognizes said peptide when T cell proliferation is determined ex vivo. Examples 11 and 12 show that subcutaneously administered peptides p66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19) before antigenic stimulated with rCry j2, T cell proliferation response was reduced (Fig 6).

The specification does not teach how to prevent Japanese cedar pollen allergy in *any* subject because he term "preventing" means to avert or to keep from happening as defines by Webster's II New Riverside University Dictionary on page 933 (of record). There are insufficient working examples using *any* peptide mentioned above for "preventing" cedar pollen allergy from *any* individual since HLA class II molecules in human are very diverse and polymorphic. Hoyne *et al* (of record) teach the success of peptide based hyposensitization therapy depends on the decrease of T cell response such as a decrease in Th2 type cytokine production by allergen specific Th cells or allergen derived peptide that are recognized by specific CD4+ T cells. There are a number of problems that need to be addressed before peptides can make the transition from experimental systems to clinical application such as peptides containing immunodominant epitopes are more potent tolergens than those containing minor epitopes. In order to obtain information on the distribution of immunodominant T cell epitopes for a particular allergen, it will be necessary to perform detailed epitope analysis on the peripheral repertoire of a large panel of allergic patients of known HLA haplotypes (See page 184, second paragraph, in particular).

Given the diverse HLA class II molecules in humans, there are insufficient working examples demonstrating that any peptide mentioned above could prevent Japanese cedar pollen allergy. Further, only two specific rCry j2 peptides induce hypo-response to the specific allergen. There is insufficient guidance that treating a subject with a Cry j1 peptide could "prevent" Japanese cedar pollen allergy from Cry j2 cedar allergen and vice versa. Further, the results in Figure 6 show that pretreatment with peptide #48 **reduce** T cell uptake of tritiated thymidine in some animal but not all animal compared with the control even in a subject with defined genetic background. Further, there is insufficient guidance with regard to the dosage of the claimed peptides as a method for "prevent" Japanese cedar pollen allergy in a subject such as a human subject. Although the specification discloses that mice were sensitized to the peptides by injecting 0.3mg in 100μl in a five-day interval, there is no disclosure about the effective therapeutic amount for the human subject. If one skill in the art were applied what is disclosed in the instant specification to human, the body weight of an average mouse is about 20 g and the body weight of a person is about 50 kg (50,000 g), one would have to inject 750 mg in a five day interval.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Applicants' arguments filed 9/11/02 have been fully considered but are not found persuasive.

Applicants' position is that Examples 11 and 12 adequately support the "preventive" effect. The T cells of the cedar pollen allergy model CB6F1 created in Example 10 recognize pj66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19), which are two major T cell epitopes of cedar pollen allergy patients. The specification shows that when these epitopes were separately administered to CB6F1 mice prior to a challenge with recombinant Cryj2 allergen the proliferation response of Cry j2-specific T cells was significantly suppressed compared with the controls (example 11 and 12).

However, the results in Figure 6 show that pretreatment with peptide #48 **reduce** T cell uptake of tritiated thymidine in some animal but not all animal compared with the control even in a subject with defined genetic background. Pretreatment with peptides such as SEQ ID NO: 14 and SEQ ID NO: 19 induces hyposensitization to the specific allergen such as Cry j2 in the subject and thereby reduces T cell proliferation upon recognition of the specific allergen. There

is insufficient working example on other peptides other than SEQ ID NO: 14 and 19 from Cry j2, much less prevent Japanese cedar pollen allergy associated with Cry j1.

7. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for a method for "preventing" Japanese cedar pollen allergy in a subject as recited in claim 16.

The specification discloses only (1) a method for identify T cell epitope in Cry j 1 and Cry j 2 using T-cell clone derived from patients who suffer from cedar pollen allergy and the T-cell response is determined by tritiated thymidine incorporation and (2) a method for treating Japanese cedar pollen allergy by identifying HLA class II molecule expressed by the subject, selected the appropriate antigenic peptide such as SEQ ID NO: 1, 5, 7, 9, 10, 21, 23, 142, 2, 8, 15, 17, 22, 3, 4, 14, 19, 6, 12, 16, 20, 18, 13 and 19 that binds to the appropriate HLA class II molecule and administer the selected antigenic peptides such as SEQ ID NO: to the subject. Example 10 shows identification of T-cell epitope in CB6F1 mice by immunized the mice with Cry j2 peptides such as SEQ ID NO: 14 and 19 recognizes said peptide when T cell proliferation is determined ex vivo. Examples 11 and 12 show that subcutaneously administered peptides p66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19) before antigenic stimulated with rCry j2, T cell proliferation response was reduced (Fig 6).

The specification does not teach how to prevent Japanese cedar pollen allergy in *any* subject because he term "preventing" means to avert or to keep from happening as defines by Webster's II New Riverside University Dictionary on page 933 (of record). There are insufficient working examples using *any* peptide mentioned above for "preventing" cedar pollen allergy from *any* individual since HLA class II molecules in human are very diverse and polymorphic. Hoyne *et al* (of record) teach the success of peptide based hyposensitization therapy depends on the decrease of T cell response such as a decrease in Th2 type cytokine production by allergen specific Th cells or allergen derived peptide that are recognized by specific CD4+ T cells. There are a number of problems that need to be addressed before peptides can make the transition from experimental systems to clinical application such as peptides containing immunodominant epitopes are more potent tolergens than those containing minor epitopes. In order to obtain

information on the distribution of immunodominant T cell epitopes for a particular allergen, it will be necessary to perform detailed epitope analysis on the peripheral repertoire of a large panel of allergic patients of known HLA haplotypes (See page 184, second paragraph, in particular). Given the diverse HLA class II molecules in humans, there are insufficient working examples demonstrating that any peptide mentioned above could prevent Japanese cedar pollen allergy. Further, only two specific rCry j2 peptides induce hypo-response to the specific allergen such as rCry j 1. There is insufficient guidance that treating a subject with a Cry j1 peptide could "prevent" Japanese cedar pollen allergy from Cry j2 cedar allergen. Further, the results in Figure 6 show that pretreatment with peptide #48 **reduce** T cell uptake of tritiated thymidine in some animal but not all animal compared with the control even in a subject with defined genetic background. Further, there is insufficient guidance with regard to the dosage of the claimed peptides as a method for "prevent" Japanese cedar pollen allergy in a subject such as a human subject. Although the specification discloses that mice were sensitized to the peptides by injecting 0.3mg in 100μl in a five-day interval, there is no disclosure about the effective therapeutic amount for the human subject. If one skill in the art were applied what is disclosed in the instant specification to human, the weight of an average mouse is about 20 g and the weight of a person is about 50 kg (50,000 g), one would have to inject 750 mg in a five day interval.

There is inadequate written description about the dosage of any peptides mentioned above as a method for "preventing" Japanese cedar pollens allergy in a human subject. Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 9/11/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) Applicants' position is that Examples 11 and 12 adequately support the "preventive" effect. The T cells of the cedar pollen allergy model CB6F1 created in Example 10 recognize p66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19), which are two major T cell epitopes of cedar pollen allergy patients. The specification shows that when these epitopes were separately administered to CB6F1 mice prior to a challenge with recombinant Cryj2 allergen the proliferation response of Cry j2-specific T cells was significantly suppressed compared with the controls (example 11 and 12). (2) the claims have been amended.

However, there is inadequate written description about the dosage as a method for "preventing" Japanese cedar pollens allergy in a subject, much less "prevent" Japanese cedar pollen allergy associated with Cry j1 using peptides such as p66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19) from Cry j2. Although the specification discloses that mice were sensitized to the peptides by injecting 0.3mg in 100μl, there is no disclosure about the effective therapeutic amount for human subject. If one skill in the art were applied what is disclosed in the instant specification to human, the weight of an average mouse is about 20 g and the weight of a person is about 50 kg (50,000 g), one would have to inject 750 mg in a five day interval.

8. Claim 17 is allowed.

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
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December 2, 2002

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